REMARKS

The above amendments direct the claims to preferred embodiments of the elected subject matter, the treatment of rheumatoid arthritis with 1, 3 oxazoles. Claim 45 has been amended to be in independent form and includes the limitations of the claims 1 and 38, with preferred values for the moiety Z recited in claim 1. Claim 58 has been amended to correct a minor typographical error.

Double Patenting

Applicants maintain the rejection of claim 45 under the doctrine of obviousness type double patenting is premature since allowable subject matter has not been identified in this application. Applicants also maintain that the rejection is moot following the amendments to claim 45 above. It is alleged there is overlapping subject matter with claims in copending applications 09/947,761, 10/788,426, 10/848,567 and 11/932,548 and 12/181,032. However, no allegation has been made that these applications contain claims to the elected subject matter, which is allegedly patentably distinct from the remaining subject matter claimed. The obviousness type double patenting rejection based on generic claims in these copending applications is inconsistent with the restriction requirement.

Rejection Under 35 USC §112, first paragraph

Applicants maintain the specification provides *objective* enablement for the methods of claims 45 and 58, that is, a statement that the compounds defined in claims 45 and 58 are functional in all of the methods claimed, including the treatment of rheumatoid arthritis. The disclosure on page 6, line 14 through page 7, line 25, of the specification clearly includes such a statement. As indicated in the previous response, the following language appears in a portion of this disclosure: "Accordingly, these compounds are useful therapeutic agents for such acute and chronic inflammatory and/or immunomodulatory diseases as rheumatoid arthritis…"

Under *In re Marzocchi,* 439 F.2d 220, 169 U.S.P.Q. 367 (CCPA 1971), objective enablement is all that is required to satisfy the first paragraph of 35 U.S.C. §112, unless the PTO can provide reasons or evidence to doubt the statements made. No reasons or evidence have been presented to doubt the statements of objective enablement made in this application.

It is alleged that the specification does not allow one skilled in the art to practice the invention without undue experimentation in applying the factors set forth in *In re Wands* 8 USPQ 2d 1400 (CAFC 1988) at 1404. It is not necessary to perform the analysis under *In re Wands* since the Office Action has not provided any reasons or evidence to doubt the assertion of objective enablement in the specification. In any event, Applicants maintain that one of ordinary skill in the art would not have to engage in undue experimentation to perform the methods of claims 45 and 58 and further maintain that the invention has not been correctly interpreted under the factors set forth in *In re Wands.*

Nature of the Invention and Breadth of the Claims

In the analysis provided in the office action it is assumed that claims are directed to methods for treating a disease mediated by p38 while they have been restricted to treating rheumatoid arthritis. In addition, the above amendments have reduced the scope of the compounds recited in the claims to preferred isoxazoles. In that the nature of the invention has not been properly characterized, many of the remaining factors such as the state of the art, the predictability in the art and the relative skill of those in the art, have not been properly analyzed.

The compounds of the present invention having shown the ability to inhibit p38 would be effective for treating rheumatoid arthritis. The office action still does not adequately address the issue of why rheumatoid arthritis could not be treated by disrupting the p38-signaling pathway.

With respect to the breadth of the claims, it is important to note that a determination of undue experimentation must be considered on a *compound by compound* basis. The mere fact that a claim is broad does *not* mean that undue experimentation is required to determine enablement of the compounds therein. It is not undue experimentation to determine enablement for *each* compound in the scope of the claim. See, for example, *In re Colianni*, 195 U.S.P.Q. 150 (CCPA 1977). One of ordinary skill in the art can easily determine, with the protocols given in the specification, whether a given compound has the utility stated. Thus, the mere fact that many compounds must be tested is not dispositive of lack of utility.

State of the Prior art

It is acknowledged that clinical studies have linked TNF-α production to a number of

inflammatory and/or immunomodulatory diseases. This has not been found to be sufficient to enable the claimed methods on the basis that, "There is no indication that such a link actually translates to treatment of the disease."

However, based on the Johns Hopkins Arthritis center website (http://www.hopkins-arthritis.org/arthritis-info/rheumatoid-arthritis/rheum_treat.html#tnfs), "There are currently three TNF inhibitors FDA approved for the treatment of RA (listed in order of their approval for RA): etanercept (Enbrel®), infliximab (Remicade®), and adalimumab (Humira®). Of these three etanercept (Enbrel®), was approved prior to the December 1998 filing date of this application. According to the website, http://pharmamotion.com.ar/mechanism-of-action-indications-and-adverse-effects-of-etanercept-infliximab-and-adalimumab, "the first approved TNF alpha blocker was etanercept (Enbrel) in May 1998. Then came infliximab (Remicaid) in November 1999, while adalimumab (HUMIRA) was approved in December 2002." Clearly the efficacy of TNFα inhibitors in treating diseases was known in the art at the time of the December 1999 filing date.

The office action concludes a link between TNF α production and rheumatoid arthritis does not mean any inhibition of TNF-α would treat rheumatoid arthritis. No reasons or evidence have been provided for finding differentiation in TNF-α inhibitors and no basis has been given for assuming the TNF-α inhibition achieved with the compounds recited in claims 45 and 58 would not be effective in treating rheumatoid arthritis.

Guidance of the Specification

The guidance provided by the specification has not been properly interpreted. The specification actually provides more than it needs to in satisfying the requirements of 35 USC §112, first paragraph. For example, general and specific methods for preparing the compounds are given on pages 21-23, pages 27-71 and in the Examples. Dosage forms, dosage ranges and methods for administering the compounds are given on pages 23-26. Methods for assessing the activity of the compounds via *in vitro* raf kinase assays (and IC_{50} data) and *in vivo* assays are provided on pages 103 and 104. The specification also discloses that inhibitors of p38 are active in animal models of TNFα production, including a murine lipopolysaccharide (LPS) model of TNFα production, in the text on page 5 of the specification which follows:

Inhibitors of p38 are active in a number of standard animal models of inflammatory

diseases, including carrageenan-induced edema in the rat paw, arachadonic acid-induced edema in the rat paw, arachadonic acid-induced peritonitis in the mouse, fetal rat long bone resorption, murine type II collagen-induced arthritis, and Fruend's adjuvant-induced arthritis in the rat. Thus, inhibitors of p38 will be useful in treating diseases mediated by one or more of the above-mentioned cytokines and/or proteolytic enzymes.

The specification also provides a number of publications which have linked TNFα production and/or signaling to a number of diseases including rheumatoid arthritis and or have linked excess or undesired matrix-destroying metalloprotease (MMP) activity to diseases such as rheumatoid arthritis. One skilled in the art need only routinely assay the compounds of formula I to confirm the activity of such a compound. Such assays are routine. The specification identifies the exemplified compounds as having IC50 values in the range specified. Contrary to the position taken in the office action, the specification does disclose how to determine whether a disease or disorder can be treated with a compound of formula I. One skilled in the art need only routinely test the activity of compounds within the scope of formula I using the assay described in the application.

Predictability or Unpredictability of the Art

No evidence has been presented that the art of treating rheumatoid arthritis with pharmaceuticals is any more predictable or unpredictable than that of other pharmaceuticals. No evidence has been presented that the potential for adverse reactions and drug interactions can not be determined routinely through conventional methods. Even if unpredictability in this art is high, absolute predictability is not required. One of ordinary skill in the art is provided the tools herein in order to determine whether a given compound is functional in the methods claim.

Working Examples

With respect to working examples, it is well established that working examples are *not* required to provide enablement. See, for example, *In re Borkowski*, 164 U.S.P.Q. 642 (CCPA 1970.

Quantity of experimentation

It would not be necessary for one skilled in the art to determine every known disease associated with p38 to practice the claimed invention since the claims are directed to treating rheumatoid arthritis. Furthermore, diseases mediated by p38 are well known to those skilled in the

art, as discussed in the background section of the specification.

Conclusion

Accordingly, it is submitted that the *Wands* factors clearly do not result in a conclusion of undue experimentation. In addition, no evidence has been presented that any of the methods claimed would not be effective in treating rheumatoid arthritis which requires an analysis of the factors in *In re Wands*. Only unsupported allegations and conclusions regarding the state of the art are provided.

For the reasons discussed above, Applicants submit that all pending claims meet the requirements of 35 U.S.C. § 112, first paragraph.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

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